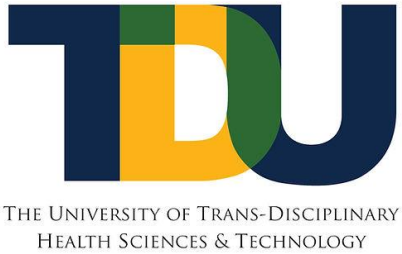
INVESTIGATING THE ROLE OF TRANSCRIPTION FACTOR 4 (TCF4) IN ADULT NEURAL STEM CELLS

THE UNIVERSITY OF TRANS-DISCIPLINARY HEALTH SCIENCES AND TECHNOLOGY



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Synopsis

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Synopsis

The phenomenon of production of new neurons in adulthood is called adult neurogenesis. The brain was considered a post-mitotic organ for a long time[1] until Gopal Das and Altman discovered proliferating cells in adult rat brains in the 1960s[2–4]. Further, studies confirmed the functional integration of these adult-born neurons and their association with learning[5]. In 1998, a study showed the first evidence of adult neurogenesis in the human brain[6]. Later, subsequent studies supported the existence of adult neurogenesis in human[7–11], but recent findings created a controversies regarding existence of adult neurogenesis in human[12–15]. Soon after, this controversy was counteracted by number of studies which showed robust evidence of persistent adult neurogenesis in human[16–19]. These discrepancies raised important technical questions, regarding human brain sample sensitivity towards method of preservation and histological detection. Subtle variations in preservation can lead to variability of results in studying adult neurogenesis in human brain.

Adult neural stem cells (NSC) reside in specific locations in the adult brain called neurogenic niches. The adult mouse brain has two major neurogenic niches: the sub-ventricular zone (SVZ)[20] and the sub granular zone (SGZ)[21–23]. In SVZ, the neural progenitors are positioned on the sub-ventricular wall lining. These NSC give rise to neuroblasts which migrate to the olfactory bulb via the rostral migratory stream, where they finally differentiate[24] into inhibitory neurons and participate in the olfactory circuit[25]. SGZ is present within the dentate gyrus in the hippocampus. Hippocampal neurogenesis in SGZ is conserved across mammalian species[22,26–32] and found in the adult human brain[6–8,10,11,16–18,] . In adult hippocampal neurogenesis, the adult NSC give rise to newborn excitatory granule neurons, which ultimately integrate and contribute to the functioning of the hippocampal circuitry[34–36]. Adult hippocampal neurogenesis is vital for learning memory[37,38], mood regulation[30], and has been implicated in pattern separation[31], and stress resilience[39].

Adult neurogenesis is sensitive to intrinsic and extrinsic environmental conditions[40,41]. Hormones like corticosterone have a negative impact on adult neurogenesis[42], whereas testosterone is known to enhance neurogenesis in birds[43,44]. Other than systemic factors, adult neurogenesis is also sensitive to stress[45], neurodegeneration[19], and voluntary exercise[41]. Adverse conditions like stress, aging, and neurodegeneration reduce adult neurogenesis[19,45–48]; in contrast, enriched environmental conditions and voluntary exercise enhance the production of newborn neurons[21,41]. All these evidences suggest a dynamic molecular machinery in adult neural stem cells for active regulation of adult neurogenesis in these various contexts. However, the molecular principles for regulating adult neurogenesis during varied physiological conditions largely remain elusive.

To better understand the molecular regulation in adult neural stem cells, we investigated the role of the transcription factor Tcf4, which showed high expression in the SGZ region in preliminary data from our lab. Also, studies have shown that Tcf4 can influence super-enhancers in neural stem cells[49], and regulate NSC differentiation in SVZ[50]. The essential role

of Tcf4 in brain development has been established by multiple studies[50,51]. These studies carried out in embryonic brains and cell lines demonstrate a regulatory role of Tcf4 in neural stem cells. Data from our lab suggested that Tcf4 continues to be expressed in adult NSC, but its function in adult NSC remained unknown. Tcf4 is clinically associated with neurodevelopmental and psychiatric disorders. Haplo-insufficiency of Tcf4 causes Pitt-Hopkins syndrome (PTHS). This neurodevelopmental disorder manifests as developmental delay, intellectual disability (ID), and cognitive deficits[52]. In addition, genome-wide association studies in Schizophrenia patients have identified Tcf4 as a high-risk allele where mutations were found in the intronic regions of the Tcf4 locus[53]. To understand the significance of continual expression of Tcf4 in the adult neural stem, we adopted an inducible loss-of-function strategy to generate inducible conditional Tcf4 deletion/knock-out (icKO), specifically in adult neural stem cells.

The first chapter of my dissertation describes our observations regarding inducible loss-of-function of Tcf4 in adult neural stem cells in vitro[54]. The second chapter consists of preliminary observations regarding the physiological relevance of Tcf4-mediated regulation of adult neural stem cells during physiological stress.

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